Modelling sub-clinical vCJD infection in the UK population

https://www.neurodegenerationresearch.eu/survey/modelling-sub-clinical-vcjd-infection-in-the-uk-population/

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Country

United Kingdom

Title of project or programme

Modelling sub-clinical vCJD infection in the UK population

Source of funding information

NIHR (PRP (ST-01-03) Modelling sub-clinical vCJD infection in the UK population)

Total sum awarded (Euro)

€ 1,535,391

Start date of award

01/03/2015

Total duration of award in years

4.0

The project/programme is most relevant to:

Prion disease

Keywords
Research Abstract

vCJD was first reported in the UK in 1996. Since then 177 deaths from probable or definite vCJD have occurred with three related to transfusion of contaminated blood. Susceptibility to vCJD is linked with methionine/valine polymorphism at codon 129 in the *PRNP* gene with all genotyped cases of clinical vCJD being found in 129MM individuals. Two asymptomatic cases of vCJD in 129MV individuals have been reported in which PrP^{Sc} was identified in the spleen

but not the brain. Material from one spleen has now been shown to be infectious. Retrospective tonsil and appendix studies have shown evidence of the presence of PrP^{Sc} in all 129 codon genotypes and all birth cohorts from 1941 with a prevalence rate of 1 in 2000 indicating a high carrier status in the UK. It is unknown whether they represent primary or secondary infections[1].

In animal studies, prion disease pathogenesis can be influenced by a variety of factors including host genetics (codon 129 of the prion protein gene), age at infection, route of infection and immune status such as co-infections. We hypothesise that codon 129 genotype of PrP is not only linked to susceptibility but plays a role in the peripheral sequestering of disease. Furthermore, we hypothesise that movement of infection from the periphery to the CNS is influenced by a variety of factors. We aim to determine if age of the individual and route of infection influences disease pathogenesis and whether codon 129 genotype of PrP plays a role in the process. Additionally, we aim to determine whether immune insults such as viral or systemic co-infection can alter disease pathogenesis and/or onset of clinical disease.

We will utilise transgenic mouse models expressing the three human codon 129 genotypes of PrP. Mice will be inoculated with vCJD via CNS or peripheral route at different ages and tissues collected at time points through disease incubation. We will ascertain whether PrP^{Sc} is present in the peripheral tissues of these mice at these time points and whether this differs between genotypes. This will be carried out using a combination of immunohistochemistry, biochemistry and infectivity studies where appropriate. A second study will use mice inoculated peripherally with vCJD and a co-infection (viral or systemic) introduced approximately 50% through disease incubation. Tissues will be collected at different time points and analysed as previously.

This study will be carried out in collaboration with NCJDRSU. Both The Roslin Institute and NCJDSRU have over 20 years of experience in investigating and characterising vCJD using transgenic mouse models of disease. The applicants involved in this proposal have a wealth of experience in vCJD disease pathogenesis and in the modelling of vCJD in mice and have published extensively in this area.

By identifying factors which may influence disease pathogenesis and the onset of clinical disease we will provide data which can be used to further inform and refine risk assessment models, particularly for potential secondary vCJD transmission. In turn, this will allow further development and review of existing and prospective risk reduction measures. In addition, the data from these studies will improve our understanding of vCJD pathogenesis; this may lead to quicker diagnosis thus preventing sub-clinical human-to-human transmission.

Lay Summary
Further information available at:

Types:

Investments > €500k

Member States:
United Kingdom

Diseases:
Prion disease

Years:
2016

Database Categories:
N/A

Database Tags:
N/A